combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Clearly for prior art to render an invention obvious, it must render obvious the whole invention and not merely some part of the invention (*In re Antonie* 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1997). The prior art must also be considered as a whole including parts that teach away from Applicant's invention. Applicant respectfully submits that these criteria are not met in the Examiner's rejections.

In claim 26, Applicant claims an implant composition, suitable for implantation in an animal body by injection, comprising a first component comprising a biologically active composition contained in a first delivery vehicle capable of immediately releasing said biologically active composition, and a second component comprising the same biologically active composition as in the first component contained in a second delivery vehicle capable of releasing said biologically active composition on a sustained basis. In claim 36, Applicant claims a method for delivering the same biologically active material to an animal body in both a rapid release and sustained release form comprising the steps of providing an implant comprising a first component comprising a biologically active composition contained in a first delivery vehicle capable of immediately releasing said biologically active composition, and a second component comprising the same biologically active composition as in the first component contained in a second delivery vehicle capable of releasing said biologically active composition on a sustained basis, and injecting said implant into the animal body. Thus, the purpose of Applicant's invention is to provide a composition and a method of treatment involving both immediate and sustained release of biologically active material.

Lewis discloses as his invention the use of specifically designed microparticles for delivery of an agent. He cites a formulation containing a growth promoter dispersed in a micro-particle matrix material (col. 3, lines 63-65). The microparticles must be made from known biodegradable synthetic polymers, casein, albumin, and waxes. Lewis further states that "by an appropriate selection of polymeric materials a micro-particle formulation can be made such that the resulting

micro-particles exhibit both defusional release and biodegradation release properties." (col. 4, lines 36-40) Lewis also discloses that the microparticles can be mixed by size or type to provide for a multi-phasic delivery, and that other agents may be added either in microparticle form or in conventional unencapsulated form where they are "blended with the growth promoter and provided to an animal by the method of the invention." (col. 6, lines 42-54) The process involves solubilization of polymer and active in an organic solvent system, emulsification of the solution, removal of the solvent by evaporation, and collection of the microparticles. Lewis does not provide for the use of disintegrating agents in the microparticles or any other component to cause immediate release of the active material. In fact, the product of the Lewis reference "offers the advantage of durations of action ranging from only 30 to 60 days to more than 200 days depending upon the type of microspheres selected." (col. 3, lines 22-25) Lewis does not teach immediate release, which is a required part of Applicant's invention.

Applicant's composition comprises a first component contained in a delivery vehicle capable of immediately releasing said biologically active composition upon implantation in an animal body, and a second component comprising the same biologically active composition as in the first component contained in a second delivery vehicle capable of releasing the active on a sustained basis upon implantation in an animal body. In addition, applicant's invention requires that the components be maintained as discrete, separate physical entities. The distinction between the mixture proposed by Lewis and the discrete composition of applicant is important in the practical dosing of animals. The composition of Lewis provides a fixed ratio between the growth promoter and the other drug selected. On the other hand, the composition of applicant allows for variability in the ratio since the number of pellets of each type selected for implantation can vary depending upon the needs of the particular animal.

The Lewis reference discloses microparticles containing the active agent, in solution or crystalline form, with the active agent dispersed or dissolved within the polymer. (col. 2, line 66 to col. 3, line 2) The purpose of the Lewis invention is to provide sustained release of the active agent. It also states that the polymer must be biodegradable. (col. 4, line 4) In contrast, Applicant's

invention requires both immediate and sustained release. In addition, when a polymer matrix is employed in Applicant's invention, it is not biodegradable. Thus, it is respectfully submitted that Lewis teaches away from Applicant's invention.

The Herbert reference discloses an invention that relates to the process of preparation of controlled-release microparticles by encapsulating active agents through the use of a solvent system and static mixers. The process comprises a biodegradable polymeric binder and a biologically active agent pumped through a static mixer into a quench liquid to form the microparticles. A solvent blend is used to dissolve the active agent and the polymer. It is dispersed in an aqueous solution to form an emulsion, which is then extracted to form the microparticles. In particular, Herbert teaches the use of a biodegradable polymer. (col. 5, lines 9-12) Thus, the particles produced by this method are very different from Applicant's composition. In addition, the Herbert reference does not disclose the immediate release of the active agent. It states "The products prepared by the methods of the present invention offer the advantage of duration of action ranging from 30 to more than 200 days, depending on the type of microparticle selected. In a preferred embodiment, the microparticles are designed to afford treatment to patients over a period of 30 to 60 days." As noted above, a polymer used in Applicant's invention is not biodegradable. The Herbert reference does not teach or suggest Applicant's invention, but instead teaches away from Applicant's invention.

The Okada et al. reference teaches a method of preparing a water-in-oil emulsion for generating microparticles for sustained release of a drug. Different drug-release rates are obtained by modifying the microparticle size and surface texture and structure. These methods for producing microcapsules and for obtaining sustained release of the drug are very different than those of the instant application. In addition, the Okada reference does not disclose or contemplate the addition of immediate release compositions to a prolonged release composition. There is no suggestion of effecting a differential release of the same pharmaceutically active agent via the use of discrete delivery vehicles. The Okada reference does not teach or suggest all of the limitations in the Applicant's claims because it discloses different methods, and it does not suggest obtaining

different release rates for the same drug. Furthermore, Okada teaches that biodegradable polymers are especially desirable in the practice of his invention. (col. 5, lines 25-30) Accordingly, Okada teaches away from applicant's invention.

The Stevens reference discloses an antibiotic and pharmaceutical pellet system and method for localized sustained antibiotic release as part of a single therapeutic procedure to prevent infection at the injection site. The sustained release of the antibiotic is to prevent an infection at the injection site, while the sustained release of the pharmaceutical is to treat another condition. The Stevens reference does not disclose the immediate and sustained release of the same pharmaceutical agent. Thus, it does not teach or suggest Applicant's invention because it does not disclose or contemplate the addition of immediate release compositions to prolonged release compositions containing the same pharmaceutically active agent.

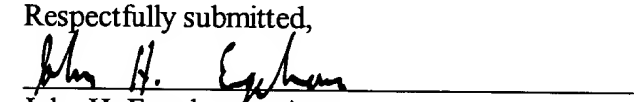
The Rickey reference discloses a method for reducing the residual processing solvent level thereby diminishing the rate of degradation of the product and increasing shelf-life. It also relates to an improved method for preparing a pharmaceutical composition in microparticle form designed for the controlled release of a drug over an extended period of time, whereby the composition exhibits increased shelf-life. This reference presents as an advantage of the products prepared by the method of production of the invention a duration of action ranging from 14 to more than 200 days, depending on the type of microparticles selected. In preferred embodiments, microparticles are designed to provide a duration of action of 30 to 60 days and from 60 to 100 days, with a duration of 90 days considered to be particularly advantageous. (Col 7, lines 44-51) This reference teaches away from the Applicant's invention when this time frame is coupled with the statement that "The exact amount of this more-rapidly-extracted solvent "spike" added to the quench liquid is of importance to final microparticle quality. Too much solvent (i.e., near the saturation point) results in porous microparticles with active agent visible on the surface, causing what may be an undesirable high rate of release." (Column 15, lines 53-58) The Rickey reference does not teach or suggest all of the limitations in the Applicant's claims because the methods for producing microcapsules and for obtaining sustained release of the drug are different than those of

the instant application. In addition, the Rickey reference does not disclose or contemplate the addition of immediate release compositions to prolonged release compositions containing the same pharmaceutically active agent.

The Guittard reference discloses osmotic devices with a semipermeable wall that is non-erodible and insoluble in fluids. Osmotically effective compounds absorb liquid from the environment and force the active agent out of the delivery device. An osmotic delivery system is not included in the claims of the instant application as amended. Additionally, Guittard teaches devices that require a considerable amount of liquid to effect delivery of the beneficial agent and thus are poorly suited for use as an implanted drug delivery system. The methods of the Guittard reference for obtaining sustained release of the active drug are very different than those of the instant application. The Guittard reference does not teach or suggest Applicant's invention because it discloses delivery vehicles that are not part of Applicant's invention.

Applicant respectfully submits that none of the references suggest Applicant's invention. There is no suggestion in any of the references which would suggest that the references be combined. Only hindsight would allow the Examiner to select bits and pieces of the prior art in an attempt to create a combination rejection. Moreover, even when combined the references do not yield Applicant's invention.

Respectfully submitted,



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APPENDIX A

(all claims)

Claims 1-25. (previously cancelled)

26. (previously amended) An implant composition, suitable for implantation in an animal body by injection, comprising:

(a) a first component comprising a biologically active composition contained in a first delivery vehicle capable of immediately releasing said biologically active composition upon implantation in an animal body and which is selected from the group consisting of encapsulants where the coating wall material is highly soluble in body fluids, porous or freeze-dried solid compositions, solid tablets or pellets containing a disintegrating agent which causes the solid tablet or pellet to rapidly break down when in body fluids, solid tablets or pellets containing said biologically active material in fine or micronized particle sizes and mixtures thereof; and

(b) a second component comprising the same biologically active composition as in component (a) contained in a second delivery vehicle capable of releasing said biologically active composition on a sustained basis upon implantation in an animal body and which is selected from the group consisting of encapsulated solutions or suspensions, biodegradable solid substances, conventional tablet/pellet ingredients, conventional tablet/pellet ingredients coated with a polymeric membrane to control release, conventional tablets or pellets containing said biologically active material having large particle sizes, matrix-tablets based on gel-forming excipients, matrix-type systems based on non-biodegradable polymers, membrane-type systems based on non-biodegradable polymers, matrix-type systems based on biodegradable polymers, matrix-type systems implant based on lipidic excipients, and mixtures thereof.

27. (previously added) The implant composition of claim 26 wherein the first delivery vehicle comprises solid tablets or pellets containing a disintegrating agent and wherein the second vehicle comprises solid tablets or pellets not containing a disintegrating agent.

28. (previously added) The implant composition of Claim 27, wherein said disintegrating agent is selected from the group consisting of sodium crosscaramellose, microcrystalline cellulose, sodium carboxymethyl-cellulose, alginic acid, starch, potassium polacrilin, colloidal silicon dioxide, crospovidone, guar gum, magnesium aluminum silicate, methyl cellulose, powdered cellulose, pregelatinized starch, sodium starch glycolate and sodium alginate and mixtures thereof.

29. (previously added) The implant composition of Claim 26 wherein said biologically active composition is selected from the group consisting of enzymes or other organic catalysts, ribozymes, organometalics, proteins and glycoproteins, peptides, poly(amino acids), antibodies, nucleic acids, steroids, antibiotics, antimycotics, anti-narcotics, cytostatics, cytotoxics, cytokines, carbohydrates, oleophobics, lipids, antihistamines, laxatives, vitamins, decongestants, gastrointestinal sedatives, anti-inflammatory substances, antimanics, anti-infectives, coronary vasodilators, peripheral vasodilators, cerebral vasodilators, psychotropics, stimulants, anti-diarrheal preparations, anti-anginal drugs, vasoconstrictors, anticoagulants, antithrombotic drugs, analgesics, antipyretics, hypnotics, sedatives, antiemetics, antinauseants, anticonvulsants, neuromuscular drugs, hyperglycemic and hypoglycemic agents, antivirals, antineoplastics antidepressants, anticholinergics, antiallergic agents, antidiabetic agents, antiarrythmics, antihormones, antihistamines, β-blockers, cardiac glycosides, contraceptives, contrast materials, radiopharmaceuticals, dopaminergic agents, lipid-regulating agents, uricoscurics, tranquilizers, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, microorganisms, viruses, releasing factors, growth factors, hormones, antihelmentics, steroids, and mixtures thereof.

30. (previously added) The implant composition of Claim 29 wherein said biologically active composition comprises a steroid, a hormone or mixtures thereof.

31. (previously added) The implant composition of claim 30 wherein said biologically active composition comprises melengestrol acetate, a combination of melengestrol acetate and trenbolone acetate or a combination of melengestrol acetate, trenbolone acetate and estradiol.

32. (previously added) The implant composition of Claim 31, wherein the melengestrol acetate is contained in each delivery vehicle in an amount of from about 5 to about 200 mg per delivery vehicle.

33. (previously added) The implant composition of claim 26 wherein either component (a) or component (b) or both further comprises one or more of the following materials: standard granulating aids, lubricants, diluents, binders and glidants, magnesium stearate, stearic acid, colloidal silicon dioxide, talc, titanium dioxide, magnesium, calcium and aluminum salts, lactose, cyclodextrins and derivatives thereof, starches, povidone, high molecular weight polyethylene glycols and derivatives thereof, bioerodible polymers and co-polymers, polystearates, carboxymethyl cellulose, cellulose, N,N-diethylamine acetate, polyvinyl alcohol, hydroxypropyl methyl cellulose, other biologically active or inactive substances or other pharmaceutically active or inactive substances.

34. (previously added) An implant composition consisting essentially of:

(a) a first component comprising melengestrol acetate contained in one or more pellets or tablets capable of immediately releasing said melengestrol acetate upon implantation in an animal body, said pellet or tablet containing a disintegrating agent; and

(b) a second component comprising melengestrol acetate contained in one or more pellets or tablets capable of releasing said biologically active composition on a sustained basis upon implantation in an animal body, said pellet or tablet not containing a disintegrating agent;

wherein said implant composition is implanted in an animal body by injection.

35. (previously amended) The implant of claim 34, suitable for administration by a single injection, consisting essentially of one to four pellets of type (a) and four to six pellets of type (b).

36. (currently amended – as presented in 27 March 2002 Continued Prosecution Application) A method for delivering the same biologically active material to an animal body in both a rapid release and sustained release form comprising the steps of:

(1) providing an implant comprising:

(a) a first component comprising a biologically active composition contained in a first delivery vehicle capable of immediately releasing said biologically active composition upon implantation in an animal body and which is selected from the group consisting of encapsulants where the coating wall material is highly soluble in body fluids, porous or freeze-dried solid compositions, solid tablets or pellets containing a disintegrating agent which causes the solid tablet or pellet to rapidly break down when in body fluids, solid tablets or pellets containing said biologically active material in fine or micronized particle sizes and mixtures thereof; and

(b) a second component comprising the same biologically active composition as in component (a) contained in a second delivery vehicle capable of releasing said biologically active composition on a sustained basis upon implantation in an animal body and which is selected from the group consisting of encapsulated solutions or suspensions, biodegradable solid substances, conventional tablet/pellet ingredients, conventional tablet/pellet ingredients coated with a polymeric membrane to control release, conventional tablets or pellets containing said biologically active material having large particle sizes, matrix-tablets based on gel-forming excipients, matrix-type systems based on non-biodegradable polymers, membrane-type systems based on non-biodegradable

polymers, matrix-type systems based on biodegradable polymers, matrix-type systems implant based on lipidic excipients and mixtures thereof; and

(2) injecting said implant into the animal body.

37. (previously added) The method of Claim 36 wherein the first delivery vehicle comprises solid tablets or pellets containing a disintegrating agent and wherein the second vehicle comprises solid tablets or pellets not containing a disintegrating agent.

38. (previously added) The method of Claim 37, wherein said disintegrating agent is selected from the group consisting of sodium crosscaramellose, microcrystalline cellulose, sodium carboxymethyl-cellulose, alginic acid, starch, potassium polacrilin, colloidal silicon dioxide, crospovidone, guar gum, magnesium aluminum silicate, methyl cellulose, powdered cellulose, pregelatinized starch, sodium starch glycolate and sodium alginate and mixtures thereof.

39. (previously added) The method of Claim 36, wherein said biologically active composition is selected from the group consisting of enzymes or other organic catalysts, ribozymes, organometalics, proteins and glycoproteins, peptides, poly(amino acids), antibodies, nucleic acids, steroids, antibiotics, antimycotics, anti-narcotics, cytostatics, cytotoxics, cytokines, carbohydrates, oleophobics, lipids, antihistamines, laxatives, vitamins, decongestants, gastrointestinal sedatives, anti-inflammatory substances, antimanics, anti-infectives, coronary vasodilators, peripheral vasodilators, cerebral vasodilators, psychotropics, stimulants, anti-diarrheal preparations, anti-anginal drugs, vasoconstrictors, anticoagulants, antithrombotic drugs, analgesics, antipyretics, hypnotics, sedatives, antiemetics, antinauseants, anticonvulsants, neuromuscular drugs, hyperglycemic and hypoglycemic agents, antivirals, antineoplastics antidepressants, anticholinergics, antiallergic agents, antidiabetic agents, antiarrythmics, antihormones, antihistamines, β-blockers, cardiac glycosides, contraceptives, contrast materials, radiopharmaceuticals, dopaminergic agents, lipid-regulating agents, uricoscurics, tranquilizers, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and

nutritional additives, antiobesity drugs, microorganisms, viruses, releasing factors, growth factors, hormones, antihelmentics, steroids, and mixtures thereof.

40. (previously added) The method of Claim 39 wherein said biologically active composition comprises a steroid, a hormone or mixtures thereof.

41. (previously added) The method of Claim 40 wherein said biologically active composition comprises melengestrol acetate, a combination of melengestrol acetate and trenbolone acetate or a combination of melengestrol acetate, trenbolone acetate and estradiol.

42. (previously added) The method of Claim 41, wherein the melengestrol acetate is contained in each delivery vehicle in an amount of from about 5 to about 200 mg per delivery vehicle.

43. (previously added) The method of Claim 36, wherein said animal is selected from the group consisting of cows, horses, sheep, swine, dogs, cats and humans.

44. (previously added) The method of Claim 43, wherein said animal is a heifer.

45. (previously added) The method of Claim 36 wherein said implanting step is selected from the group consisting of subcutaneous, intramuscular, intraperitoneal, and intracranial injections.

46. (previously added) The method of Claim 45 wherein said animal is a heifer and said implanting step comprises subcutaneous injection in the posterior of the ear of said heifer.

47. (previously amended) The method of Claim 36 wherein step (2) comprises a single injection.